

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Longitudinal follow up of employment status in patients with chronic fatigue syndrome after mononucleosis
AUTHORS	Nyland, Morten ; Naess, Halvor; Birkeland, Jon; Nyland, Harald

VERSION 1 - REVIEW

REVIEWER	Ben Katz Professor of Pediatrics Northwestern University Feinberg School of Medicine Attending Physician Division of Infectious Diseases Lurie Children's Hospital Chicago, IL
REVIEW RETURNED	12-Jun-2014

GENERAL COMMENTS	<p>I think this is a good study. However, the Results are a bit hard to follow and I think some additional analyses should be done. Discussion is also a bit long. See the Comments to Authors. I would advise a resubmission.</p> <p>Introduction:</p> <ol style="list-style-type: none">1. I do not understand why all of the 8 characteristics of CFS listed in paragraph 1 are not analyzed in the paper, especially in Tables 1-4.2. How was mono diagnosed? Self-report? Physician report? Lab testing?3. A description of or a reference to the "written self management program ... including active coping strategies" should be included in the Methods. <p>Results:</p> <ol style="list-style-type: none">1. Does the number of patients at Contact 1 (111) include all of the patients in the Norwegian database with CFS following mono?2. I cannot trace all of the patients. For example, at the time of mononucleosis (which is years before Contact 1) we are told of 43 employed and 48 students = 91. At Contact 1, we are told of 9 employed, 12 students and 70 neither = 91. What happened to the other 20 patients? Also, at Contact 1 we are told that 1 was receiving partial DP, 7 full DP, 14 partial long-term sickness absence benefits and 62 full long-term sickness absence benefits = 84. What about the other 27 patients?3. Similarly at Contact 2 we are told of 24 employed full time, 25 part time, 40 unemployed and 1 student = 90, while there should be 92 patients at Contact 2. We are also told of 15 on partial DP, 39 on full DP, 6 partial sickness benefits and 3 full sickness benefits = 63; does this mean the other 29 were not receiving benefits?4. Last paragraph on page 10: Why were 2 regression analyses
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	<p>necessary?</p> <p>5. P. 11, 1st paragraph: Did FSS score at Contact 1 correlate with post-exertional malaise? I am not sure what the authors mean by "mode of onset of fatigue after mononucleosis (acute or taking months)". Was there any correlation between Concentration problems at Contact 1 and unemployment at Contact 2?</p> <p>6. p. 12, 1st sentence needs to be clarified. Perhaps adding the words "worse scores on" after "associated with" will help.</p> <p>7. p. 12, last sentence: How is lack of education statistically significant if the p value is only 0.21?</p> <p>Discussion</p> <p>In general is a bit long. See below.</p> <p>1. p. 15, 1st sentence: I would change "children" to "younger individuals".</p> <p>2. p. 15, 1st paragraph, 3rd sentence; I would change "are probably" to "may be".</p> <p>p. 15, 2nd paragraph: Arthralgia may be a predictor, but it did decrease in those who improved. Also, since it was present in about half of patients at Contact 1 it will not be too discriminatory.</p> <p>3. p. 16, 1st paragraph: I would add the words "Pre existing" to the beginning of sentence 2 and delete sentence 3.</p> <p>4. p. 16, 2nd paragraph: I would delete the 3rd and 4th sentences.</p> <p>5. p. 16, 3rd paragraph: I would change "is probably" to "may be" in sentence 2. I would add patient heterogeneity as a possible factor in explaining differences between studies. Finally, I would delete the last sentence.</p> <p>6. p. 16, last paragraph: 2nd sentence is redundant and can be deleted; I would also delete the 3rd and 4th sentences. Authors should add that a difference in their study is a uniform trigger (mononucleosis) in all the patients.</p> <p>7. Page 17, last sentence: I would add the words "persistence of" before "arthralgia".</p> <p>Table 2:</p> <p>1. I do not understand how the FSS score (mean) is the same in both those with FSS < 5 and those with FSS > 5 (unless the medians were markedly different from the means).</p> <p>2. Did those who were already improved at Contact 1 continue to get better or were the ones who improved between Contact 1 and Contact 2 from the No change or Worsening groups at Contact 1?</p> <p>Table 4:</p> <p>1. I am not sure what "Beta" means.</p> <p>2. Why are there different variables in this Table (especially Education) from the previous tables? It seems to me that the same variables should be analyzed at all time points. See also Introduction, Comment 1.</p> <p>There are also a few typo's:</p> <p>1. p. 7: "do" should be "does" in line 36</p> <p>2. p. 7: "lover" should be "lower" in line 50</p> <p>3. Page 15, line 39: "initiate" should be "initiates".</p>
REVIEWER	Henrik Horwitz The Department of Clinical Pharmacology, Bispebjerg Hospital, University of Copenhagen
REVIEW RETURNED	15-Sep-2014

GENERAL COMMENTS	<p>This is an interesting and important study about a controversial disease. In my opinion data could have been presented with more enthusiasm.</p> <p>Language: Needs a bit of language editing</p> <p>Introduction: Maybe some points about the historical perspectives of CFS could be beneficial to the manuscript. Furthermore, some general public health/insurance perspectives could be relevant.</p> <p>Methods: Very good</p> <p>Results: This section is a bit lengthy and disorganized. Maybe some subheading could be valuable.</p> <p>Furthermore, I recommend some kind of graphical presentation of your data.</p> <p>Questions:</p> <ol style="list-style-type: none"> 1) Only 83 % of the patients completed follow-up. What happened to the remaining 17 % - were they still alive? 2) Is it possible to predict who will become chronically disabled on the basis of your data. Could you create a multivariate prediction model? 3) Can you create a “time to re-employment” curve <p>Discussion: Is it possible to summarize the results from previous studies in a table.</p> <p>I think this is an interesting and well-conducted study, and I hope you can use some of my suggestions.</p>
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VERSION 1 – AUTHOR RESPONSE

Respos to reviewer 1

Introduction

1. We have now added analyses including all 8 characteristics of CFS except post-exertional malaise which was not included in the questionnaires in Tables 1-3, but not Table 4 which is a linear regression analysis. We have now described the method underlying the linear regression in the methods. We have only data on post-exertional at Contact1 and we have therefore not included this variable in the tables. However, we have added a pairwise correlation analysis between post-exertional malaise (at Contact1) and FSS score at Contact2 in the Results.

2. We have now added information on what underlie the diagnosis of mononucleosis.

3. A better description of self-management is now included.

Results

1. Yes, and we now added information on this in the Methods.
2. In total 92 patients returned the questionnaire at Contact2. Therefore comparison between Contact1 and Contact2 was only possible for these 92 patients. We do not have data on employment data for those patients who did not return the questionnaire at Contact2. We do not know what happened to the 20 patients who did not return the questionnaire. We have added information on the number of patients with missing data.
3. Data as to employment was missing in three patients. We have no added information on this. It is correct that 29 did not receive any benefits.
4. One regression analysis was based on knowledge available at Contact 1 and the second regression analysis was based on knowledge available at Contact 2. We have now added information making this clearer. Including independent variables from both Contact 1 and 2 in the same multivariate analysis is ill-advised.
5. We have now added the results of the correlation analysis between post-exertional malaise at Contact 1 and FSS score at Contact 1. We have now defined "mode of onset" of fatigue more accurately. There was no correlation between employment at Contact 2 and concentration problems at Contact 1.
6. We have made changes to the first sentence on page 12 in order to make it clearer.
7. P-value in Table 4 is wrong. We have corrected the value from .21 to .021.

Discussion

1. We have made changes as suggested.
2. We have made changes as suggested.
3. We have made changes as suggested.
4. We have made changes as suggested.
5. We have made changes as suggested.
6. We have made changes as suggested.

Table 2

1. FSS means in Table two is based on FSS score on Contact 1. We have now tried to clarify this.
2. We have no added the results of the requested analyses (in the Results).

Table 4

1. In linear regression analysis, beta tells you how much the dependent variable changes for each change in the independent variable.
 2. We have now added education and psychic stress to the appropriate table.
- Typos are now corrected.

Respos to reviewer 2

Headlines in the Results are added.

Historical perspectives are now added in the first paragraph of the Introduction.

As to graphical presentation we have now added a figure showing employment rates at Contact 1 and 2.

1. We know that one is dead. Otherwise we have no data after Contact 1.
 2. Logistic regression with employment or not at Contact 2 as dependent variable shows employment to be associated with lower age, arthralgia (Contact 1), improvement prior to Contact 1 and higher education. This independent variable predicst about 30% of the employment variability (pseudo R2). This has been added to the Results.
 3. We do not have data on time to re-employment.
- We have not included a summary of the results from previous studies in at table because of the restriction of number of tables and figures in BMJ.

VERSION 2 – REVIEW

REVIEWER	Ben Katz Northwestern University USA
REVIEW RETURNED	15-Oct-2014

GENERAL COMMENTS	<p>The paper is much improved.</p> <p>Major issue:</p> <p>I still cannot trace all of the subjects.</p> <p>Employment at Contact 1. Authors should clearly state whether the N here is 91 or 111. Neither number seems to work consistently, however, since $9 + 12 + 70$ (numbers from 1st sentence) = 91, while $1 + 7 + 14 + 62 + 8$ (numbers from 2nd and 3rd sentences) = 92.</p> <p>Employment at Contact 2. Authors should state clearly here that N = 92, and this is the total of all subjects in the first sentence ($24+25+40+3$). The problem then is when the numbers beginning with the 2nd sentence are added up we only get 65 ($1+15+39+6+3+1$).</p> <p>Minor issues:</p> <ol style="list-style-type: none">1. Not sure why nearly the whole paper is in italics.2. The two paragraphs beginning with Logistic regression analyses at the bottom of p. 9 have many duplicate words (eg "atat", ""ContactContact1").3. Study is not really prospective. It is a two time point study.4. Text related to references 12 and 13 at the end of the Introduction should be a separate paragraph and moved to earlier in the Introduction (eg after paragraph 2).5. Discussion could be a bit shorter and to the point. Results from ref. 27 should be briefly summarized at the end of the 1st paragraph on p. 13. I would delete material related to references 31 and 32. Finally, I would tone down speculation re CFS being a rheumatologic condition in paragraph 2 on p. 14.6. Paper in general can use a bit of "tightening up". For example, if information about the written self-management program is added to the sentence beginning at the bottom of p. 5 the entire next sentence could be deleted.
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VERSION 2 – AUTHOR RESPONSE

Major issue

We have now added data on the total number of patients, and made better specification of the numbers to avoid misunderstanding.

Minor issue

1. We do not know why the reviewer received a version in italics.
2. We have now corrected the duplicate words.
3. We have changed from prospective to two time point study.
4. We have moved the text as suggested.
5. We have shortened the text regarding ref. 27 and deleted the text related to ref 31 and 32 as suggested. We have also toned down the speculation regarding rheumatologic condition.
6. We have shortened the text regarding the information on written self-management and further tightened the discussion as described in 5) above.

In addition, we have provided additional information as requested by the editor.